Thrombolysis is not warranted in submassive pulmonary embolism: a systematic review and meta-analysis

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ABSTRACT

Acute pulmonary embolism (PE) is a major cause of morbidity and mortality in hospitalised patients. While the vast majority of patients with PE survive, a subset die, mostly within a few hours of presentation. Anatomically massive pulmonary emboli account for only half these deaths, while submassive or recurrent embolism accounts for the other half. There are increasing reports of patients with PE, normal blood pressure and no shock who have significant right heart dysfunction. In large registry-based cohorts, patients with right ventricular dysfunction have worse clinical outcomes. Rapid anticoagulation of the haemodynamically stable patient with PE is associated with excellent outcomes. There is also evidence to support the use of thrombolysis in patients with massive PE. However, the optimal management of patients with submassive PE is controversial. This article looks at the definition and diagnosis of submassive PE, and systematically reviews the role of thrombolytic therapy in this subgroup of patients.

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The treatment and outcome of patients with pulmonary embolism (PE) are strongly influenced by the presence or absence of associated haemodynamic derangements and comorbidities. Standard treatment with heparin has been shown to improve outcome. However, in significant PE, short-term mortality remains unacceptably high — ranging from 10% to 17.5%, and higher for those with massive PE.[1,2] Thrombolysis theoretically allows rapid resolution of clot burden and pulmonary obstruction when compared with standard anticoagulation therapy, but its use remains controversial because of the attendant risk of bleeding. In patients with uncomplicated PE, standard anticoagulation therapy seems a sensible balance of competing risks, based on the available evidence.

This review addresses the role of thrombolytic therapy in submassive pulmonary thromboembolism.

What is submassive pulmonary thromboembolism?

We are familiar with patients who have a major cardiovascular collapse as a consequence of PE and face impending death. In these patients, the risk of thrombolysis may be acceptable to avoid death. But in patients whose haemodynamic status is normal (normotension and no shock), the risk balance may be different.

Submassive PE is a defined subgroup of PE, in which patients have right ventricular (RV) dysfunction on echocardiography without attendant shock or haemodynamic instability[3] (Table 1). The prevalence of RV dysfunction in PE is highly variable, with reported rates ranging from 40% to 70%.[4] However, various studies have used different definitions of RV dysfunction (Table 2).

A major issue in diagnosis of submassive PE is the lack of clear consensus on what constitutes new acute RV dysfunction. It is often identified using a technique that is clearly operator-dependent — echocardiography. The confusion and lack of an agreed "gold standard" for diagnosing RV dysfunction increases the likelihood of bias in trials looking at this problem.

What evidence links right ventricle dysfunction with poor outcome?

Patients with normal systemic arterial pressure have a relatively low risk of recurrent PE and death when treated promptly with therapeutic anticoagulation. However, those who present with hypotension, shock or cardiac arrest have a much higher mortality rate and are often given thrombolytic therapy. Recent evidence indicates that the presence of RV dysfunction identifies a subgroup of normotensive patients who also have a much more guarded prognosis.

A correlation between RV dysfunction and mortality was observed in a small randomised controlled trial of thrombolysis for PE in 1993,[5] and in the large International Cooperative Pulmonary Embolism Registry trial, which involved 2454 patients with proven PE.[6] In the latter registry-based cohort study, echocardiography was performed in 1135 (47%) patients, and RV dysfunction was seen in 963. A nearly twofold increase in mortality (hazard ratio, 1.8; 95% CI, 1.2–2.6) was seen at 3 months in the patients with RV dysfunction.

A recent systematic review assessed the prognostic value of RV dysfunction in PE. This included 1890 patients across seven trials. Results could not be pooled because of the marked heterogeneity between the trials in the way RV dysfunction was quantified. However, the review found up to a twofold increase in PE-related risk of death in the short

Table 1. Diagnostic definition of acute submassive pulmonary embolism*

- Presence of pulmonary embolism
- Absence of shock or haemodynamic collapse (systolic blood pressure > 90 mmHg)
- Absence of new-onset arrhythmia, hypovolaemia or sepsis
- Presence of right ventricular dysfunction on echocardiography

* Taskforce on Pulmonary Embolism, European Society of Cardiology.[3]

term when patients had RV dysfunction. The absolute risk varied from 4% to 18%. Notably, there were several methodological flaws in the trials that investigated this question. Ideally, studies to establish diagnostic accuracy should include an inception cohort and independent, blinded and validated outcome adjudication. Participants must be treated by clinicians who can stay blinded to results of the echocardiogram to minimise bias. Currently, the evidence is inconclusive about the ideal way to diagnose this problem.

Due to the vagaries of diagnosing RV dysfunction and the lack of good evidence that RV dysfunction is a well-validated surrogate outcome measure, the mere presence of so called "RV dysfunction" may not necessarily select a subgroup of patients who will have poor outcomes. The problem is that we just do not know. Verification bias and other poor diagnostic trial methodology may account for the apparent association of RV dysfunction with poor outcomes.

Does thrombolysis improve clinical outcome of patients with submassive PE?

The use of thrombolytics to alleviate the impediment to RV ejection and expand the vascular bed is a logical extrapolation of their potential role in PE. Reports of the efficacy of these agents in clot lysis have appeared in the literature for over three decades. However, whether this translates to decreased mortality and morbidity remains questionable.

To answer this question, I conducted a systematic review of Medline, EMBASE and the Cochrane Library (from inception to April 2007), using the search terms pulmonary embolism, thrombolysis, thrombolytic therapy, fibrinolysis, and specific names of thrombolytic agents (streptokinase, urokinase [Abbokinase], tissue plasminogen activator [tPA] or recombinant tissue-type plasminogen activator [rt-PA], alteplase, prourokinase [Umbralina] and urokinase), combined with sensitive filters for meta-analysis and randomised controlled trials. No language restrictions were placed, to avoid publication bias.

The review included all trials that:

- included patients with submassive PE;
- involved a randomised comparison of thrombolytics; and
- reported on clinical outcomes of mortality and bleeding.

Publication bias was assessed using a funnel plot analysis. Heterogeneity was formally assessed, and, in its absence, the results when appropriate were pooled (risk ratio) using a random effects (DerSimonian and Laird weighting method) model.[11]

Study selection and analysis

> "The principal difficulty in your case", remarked Holmes, in his didactic fashion, "lay in the fact of there being too much evidence. What was vital was overlaid and hidden by what was irrelevant".
>
> *Memoirs of Sherlock Holmes. The naval treaty*, Arthur Conan Doyle, 1893.

The search identified five meta-analyses[12-16] and 11 primary trials.[5,7,17-25] Restricting the search to trials that recruited patients with normal haemodynamic parameters left six trials.[5,18,19,21,22,24] Only two of these routinely performed echocardiography to ascertain RV dysfunction,[5,21] and only one focused on submassive PE.[21] The trials were published between 1988 and 2002. There was no clear evidence of publication bias on funnel plot analysis. As there was no significant heterogeneity between these trials, they were combined to give a pooled estimate.

Study design

A total of 494 patients underwent evaluation of thrombolytic therapy. All studies were randomised comparisons, and all but two[22,24] randomised patients in a 1 : 1 ratio. One trial

Table 2. Diagnostic criteria for right ventricular dysfunction on echocardiography*

- Qualitative hypokinesis of the RV wall
- Paradoxical systolic septal motion
- Dilatation of the RV cavity (apical, subcostal or transoesophageal four-chamber views)
- RV end-diastolic diameter > 30 mm (precordial views)
- RV–LV end-diastolic diameter ratio > 1 (four-chamber view)
- Presence of pulmonary hypertension (Doppler acceleration time < 90 ms or RV–atrial gradient > 30 mmHg) in the absence of RV hypertrophy (free wall thickness > 7 mm)
- Presence of any of following criteria:
  - Tricuspid regurgitation with jet velocity > 2.8 m/s
  - Tricuspid regurgitation with jet velocity > 2.5 m/s in the absence of IVC collapse on inspiration
  - Dilatation of the right pulmonary artery > 12 mm/m^2
  - Right ventricular wall thickness > 5 mm
  - Loss of inspiratory IVC collapse

* This is a collection of differing variables reported in various studies.[5-10]
RV = right ventricle. LV = left ventricle. IVC = inferior vena cava.

Table 3. Characteristics of randomised studies of thrombolysis in pulmonary embolism (PE)

Trial and year	No. of patients	Lead time (days)*	PE diagnosis	Thrombolytic regimen	Primary outcome	Follow-up
Marini[24] 1988	30 (10 in each group)	< 7	PAng, V/Q scan	Heparin or urokinase 800 000 U every 12 h for 3 days or urokinase 330 000 U for 12 h	Reperfusion on V/Q scan	12 months
Levine[22] 1990	58 (25 heparin, 33 rt-PA)	< 14	PAng, V/Q scan	Heparin or rt-PA (0.6 mg/kg) for 2 min	Reperfusion on V/Q scan	10 days
PIOPED[18] 1990	13 (4 heparin, 9 rt-PA)	< 7	PAng, V/Q scan	Heparin or rt-PA (40–80 mg) for 40–90 min	Pulmonary artery pressure on PAng	7 days
PAIMS2[19] 1992	36 (16 heparin, 20 rt-PA)	< 10	PAng	Heparin or rt-PA 100 mg (front-loaded, 10–50–40 mg) over 2 h	Reperfusion on PAng and haemodynamics	20 days
Goldhaber[5] 1993	101 (55 heparin, 46 rt-PA)	< 14	PAng, V/Q scan	Heparin or rt-PA 100 mg over 2 h	RV dysfunction on echocardiogram	14 days
Konstantinides[21] 2002	256 (138 heparin, 118 rt-PA)	< 4	PAng, V/Q scan, or CTPA + RV dysfunction	Heparin or rt-PA 100 mg (front-loaded, 10–90 mg) over 2 h	Death or clinical deterioration	30 days or hospital discharge

* Maximum time from diagnosis to randomisation. rt-PA = recombinant tissue plasminogen activator. PAng = pulmonary angiography. V/Q = lung ventilation perfusion. CTPA = computed tomography pulmonary angiography. RV = right ventricular. ◆

compared two doses of urokinase with heparin,[24] while the other five compared rt-PA with heparin (Table 3). All studies included an objective assessment of PE.

Study quality

Only one study[5] reported the method of randomisation and allocation concealment in sufficient detail to confidently observe that it was followed (Table 4). Allocation concealment is an important aspect of avoiding bias.[26] All studies prospectively defined clinical outcomes, and this was adjudicated in a blinded fashion in four of the six trials.[18,19,21,22]

Effect of thrombolytic therapy: mortality

No effect of thrombolytic therapy was noted on short-term mortality (Table 5A). Thrombolytic therapy did not decrease mortality when used to treat patients with PE and normotension (Table 6). Even in the largest trial, which restricted recruitment to submassive PE, no mortality benefit was seen from using thrombolytics. Death from all causes ranged from 2.2% in the thrombolytic group to 3.4% in the heparin group ($P = 0.71$).

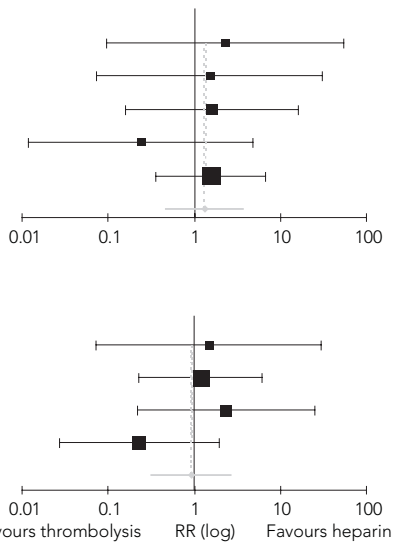
A caveat with the use of mortality as an outcome is that the duration of follow-up needs to be adequate. In all but one trial, the maximum follow-up period was 30 days. While this is likely to have captured the decreased mortality from acute right heart failure, it may have missed late deaths attributable to intracranial haemorrhage. Mortality in PE may also be influenced by the underlying cardiopulmonary reserve and presence or absence of other comorbidities; thus, thrombolysis alone may have been an insufficient strategy to influence outcome, and this may explain why no effect on mortality was seen in these trials.

Table 4. Methodological quality of randomised studies of thrombolysis in pulmonary embolism

Trial	Allocation concealment	Predefined outcomes	Blinded outcome assessment	Intention-to-treat analysis	Loss to follow-up > 5%	Baseline differences
Marini[24]	Not stated	Yes	No	Not stated	No	No
Levine[22]	Not stated	Yes	Yes	Not stated	No	No
PIOPED[18]	Not stated	Yes	Yes	Not stated	No	No
PAIMS2[19]	Not stated	Yes	Yes	Not stated	Not stated	Yes
Goldhaber[5]	Yes	Yes	No	Yes	No	No
Konstantinides[21]	Not stated	Yes	Yes	Yes	Not stated	No

Table 5. Risk ratio (RR) in randomised controlled trials of thrombolysis in cases of pulmonary embolism without haemodynamic compromise

Study	Year	Thrombolytic	Placebo	Forest plot, random effects model – risk ratio	DerSimonian and Laird weight (%)	Association measure (95% CI)
A. Mortality						
Marini (excluded)	1988	0/20	0/10		0	Excluded*
Levine	1990	1/33	0/25		10.4%	2.29 (0.10–54.05)
PIOPED	1990	1/9	0/4		11.4%	1.50 (0.07–30.59)
PAIMS2	1992	2/20	1/16		19.4%	1.60 (0.16–16.10)
Goldhaber	1993	0/46	2/55		11.4%	0.24 (0.01–4.84)
Konstantinides	2002	4/118	3/138		47.4%	1.56 (0.36–6.83)
Meta-analysis		8/246	6/248		100%	1.31 (0.47–3.62)
B. Major bleeding†						
Marini (excluded)	1988	0/20	0/10		0	Excluded‡
Levine (excluded)	1990	0/33	0/25		0	Excluded‡
PIOPED	1990	1/9	0/4		12.7%	1.50 (0.07–30.59)
PAIMS2	1992	3/20	2/16		41.6%	1.20 (0.23–6.34)
Goldhaber	1993	2/46	1/55		20.5%	2.39 (0.22–25.54)
Konstantinides	2002	1/118	5/138		25.3%	0.23 (0.03–1.97)
Meta-analysis		7/246	8/248		100%	0.94 (0.32–2.75)



* Study was excluded (did not contribute) to the final analysis as there were no deaths.
† Major bleeding was defined as intracranial haemorrhage, bleeding requiring surgery or transfusion, or fall in haematocrit > 10%.
‡ Study was excluded (did not contribute) to the final analysis as there were no episodes of major bleeding.

Effect of thrombolytic therapy: morbidity

Escalation of therapy

There has been much controversy about the benefit of thrombolytics reported in submassive PE in the trial of Konstantinides et al.[21] The authors reported on an a priori defined outcome of escalation of therapy. One category of this escalation was the use of open-label secondary thrombolysis after unblinding of participants' treatment groups. The beneficial effect of thrombolysis was seen only for this aspect of escalation of therapy. On exploring the other reported reasons for escalation of therapy, such as use of catecholamine and institution of mechanical ventilation, no differences were observed.

This raises an interesting question: when a patient's treatment group is unblinded because of worsening clinical symptoms, would the physician be less likely to administer a dose of thrombolytics if the patient had already received thrombolysis than if the patient had received only heparin?

Recurrence of pulmonary emboli

Recurrence of PE was not reported in one trial,[18] and no cases occurred in either group in another two trials.[22,24] When the remaining three trials were pooled, there was

Table 6. Efficacy and safety outcomes in the randomised studies of thrombolysis in pulmonary embolism (PE)

	Mortality (%)		Bleeding (%)*		Recurrence (%)	
Study	Heparin	Thrombolytic	Heparin	Thrombolytic	Heparin	Thrombolytic
Marini[24]	0	0	0	0	0	0
Levine[22]	0	3%	0	0	0	0
PIOPED[18]	0	11%	0	11%	NR	NR
PAIMS2[19]	6%	10%	13%	15%	19%	5%
Goldhaber[5]	4%	0	2%	4%	9%	0
Konstantinides[21]	2%	3%	4%	0.8%	3%	3%

* Major bleeding was defined as intracranial haemorrhage, bleeding requiring surgery or transfusion, or fall in haematocrit > 10%.
NR = outcome not reported.

no statistically significant difference between the thrombolytic and heparin groups with regard to preventing short-term recurrence of PE (pooled OR, 0.49; 95% CI, 0.11–0.49).

Perfusion defects on lung ventilation–perfusion scanning

Perfusion defects on lung ventilation–perfusion scanning were studied in two of the six trials. In the Goldhaber et al trial,[27] paired perfusion lung scans in 95 patients demonstrated that, on average, more than a third of lung tissue was not perfused at baseline. Compared with baseline, there was an absolute increase of 14.6% (95% CI, 10.2%–19%) in the thrombolysis group, compared with 1.5% (95% CI, 0–4.3%) in the heparin group on follow-up scan. The weighted mean difference (WMD) at the end of Day 1 in this study was 0.13% (95% CI, 0.005%–0.21%). In the PAIMS2 study,[19] there was no absolute difference at Day 7 (WMD, 1.70%; 95% CI, –1.04% to 4.44%), but, at Day 30, there was an absolute difference between the heparin and thrombolysis groups (WMD, 2.80%; 95% CI, 0.35%–5.25%). However, if these were recalculated as a difference from the respective baseline scans, the difference in lung perfusion defects was no longer seen.

Haemodynamic improvement

Two of the six trials reported on haemodynamic variables. In PIOPED,[18] the mean pulmonary artery pressure (PAP) did not differ statistically between the two groups. In the PAIMS2 study,[19] the mean PAP in the thrombolysis group decreased from a baseline of 30.2 mmHg (SD, 7.8 mmHg) to 21.4 mmHg (SD, 6.7 mmHg) after 2 hours, compared with a decrease from 22.3 mmHg (SD, 10.5 mmHg) at baseline to 21.4 mmHg (SD, 6.7 mmHg) after 2 hours in the heparin group. Pulmonary artery pressure seemed to improve more frequently in patients who received thrombolysis.

Right ventricular dysfunction

Echocardiographic improvement of RV dysfunction was studied in only one trial.[5] This study defined RV dysfunction as presence of hypokinesis (graded as mild, moderate or severe), presence of tricuspid regurgitation (qualitative on the size of the largest Doppler jet) and increased right ventricular cavity size (by planimetry). At 24 hours, RV dysfunction had improved in 39% of the thrombolysis group compared with 17% of the heparin group, while it had worsened in 2% of the thrombolysis group compared with 17% of the heparin group ($P = 0.005$). Interestingly, while the study of Konstantinides et al[21] used RV dysfunc-

Table 7. Characteristics of exclusion criteria in various randomised studies

Study	Surgery or biopsy	GI or GU bleeding	Stroke or TIA	Other exclusion criteria	Uncontrolled BP
Marini[24]	< 7 days	NS	NS	Age > 72 years	NR
Levine[22]	< 10 days	NR	< 2 months	Active bleeding process Platelet count < 100×10^9/L Heparin for > 72 h	
PIOPED[18]	NR	NR	NR	NR	NR
PAIMS2[19]	< 7 days	< 3 months	< 3 months	Puncture of non-compressible vessel Haematological disorder Contraindication to use of heparin Hepatic renal insufficiency Pregnancy	Yes
Goldhaber[5]	< 10 days	NS	< 10 days	Major internal bleeding within 6 months* Occult blood in stool Diabetic retinopathy Platelet count < 100×10^9/L Hepatic renal insufficiency Pregnancy Not expected to survive > 1 month	Yes
Konstantinides[21]	< 7 days	< 3 months	< 6 months	Trauma within 10 days Age > 80 years Diabetic retinopathy Current oral anticoagulant therapy Hepatic renal insufficiency Pregnancy Not expected to survive > 6 months	Yes

* Major bleeding was defined as intracranial haemorrhage, bleeding requiring surgery or transfusion, or fall in haematocrit > 10%.
GI = gastrointestinal. GU = genitourinary. TIA = transient ischaemic attack. BP = blood pressure. NR = not reported.

tion as an entry criterion, it did not report whether it decreased as a result of treatment.

Safety of thrombolytic therapy: bleeding

Major bleeding was seen in 15 patients across all groups in the six trials (Table 5B). Major bleeding was defined as any intracranial haemorrhage, bleeding requiring further surgery or transfusion, or a drop in haematocrit > 10%. Two studies reported no cases of major bleeding. Overall there was no difference in the incidence of major bleeding between the two groups (risk ratio [RR], 0.94; 95% CI, 0.32–2.75). It has been observed that the incidence of intracranial haemorrhage with thrombolytics in the setting of PE is less than 2%.[28,29] Admittedly, this risk varies with patient age and comorbidities. Patients who had recent surgery, biopsy or trauma were excluded from these trials, therefore limiting their external validity and applicability in common clinical situations (Table 7).

Discussion

In all trials, pooled estimates did not reveal any improved survival or increased risk of bleeding with the use of thrombolytics. Thrombolytics favourably affect RV dysfunction. Why was no significant effect seen on mortality or bleeding? It may be that RV dysfunction as currently defined is not a causal factor increasing mortality. So, altering this factor may not improve survival. Alternatively, the finding may reflect the underpowered nature of these trials. If one calculates the sample size required to show an absolute difference in major bleeding of 0.25%, assuming a baseline risk of 2%, $\alpha = 0.05$, and $\beta = 80\%$, then each arm of the trial would require over 3700 patients!

Surrogate end-points have a dubious history in medicine.[30] There are many examples in acute medicine of specific treatments that have been shown to improve surrogate outcomes but, when tested in a more clinically meaningful manner, have been shown to be deleterious. Anti-arrhythmics in acute myocardial infarction[31] and noradrenaline in cardiac arrest[32] are but two of the many. Prentice[33] developed criteria that must be fulfilled for a surrogate outcome to be a true and valid reflection of clinically meaningful outcomes. These include the need both for the surrogate to be a correlate of clinical outcome and for it to fully capture the net effect of the treatment on clinical outcome. The latter is often missing in surrogate outcomes. At best, currently available evidence supports the view that RV dysfunction resolves with thrombolysis. It is not clear whether this translates to an improvement in clinically meaningful outcomes. We must be very cautious in using improvements in surrogate outcomes when there is potential for harm. It is also not clear how thrombolysis affects persistent right heart dysfunction and lower-limb venous hypertension in these patients.

A recent modelling study[34] that used the data from these trials to determine the cost effectiveness of thrombolysis concluded that heparin is, in fact, the marginally more cost-effective approach.

Conclusions

The lack of clear mortality benefit, combined with the potential for harm and increased health care cost with the use of thrombolytics, does not favour their use in submassive PE.

A well-designed diagnostic accuracy study is first required to identify patients with submassive PE who are at increased risk. Then, an adequately powered trial on clinically meaningful outcomes is urgently needed to answer whether thrombolytics are indicated in submassive PE.

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